Computational modeling as a method to investigate the role of mechanics in cell migration through a degradable viscoelastic extracellular matrix

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Introduction: The extracellular matrix (ECM) is an important regulator of angiogenesis, the formation of new blood vessels from the existing vasculature. In order to form an angiogenic sprout, cells extend protrusions, adhere to the ECM, generate contractile forces and locally degrade the ECM. While the effect of biological signals on blood vessel formation is being investigated thoroughly, the effect of mechanics remains still largely uninvestigated. Therefore, in order to get a better understanding of the role of mechanics in angiogenic sprouting, we develop computational models with an accurate implementation of cell and ECM mechanics.

Methods: A computational model has been developed of cell migration through a viscoelastic ECM by local degradation. The ECM is modeled by means of non-inertial smoothed particle hydrodynamics (NSPH), a mesh-free numerical method in which, by discrete convolution with a smoothing kernel, the continuum laws of fluid and solid mechanics are implemented in a discrete way. In contrast to commonly used mesh-based methods, this method can deal naturally with large deformations and degradation of the ECM and migration of a cell through the ECM. A cell model is embedded in the ECM that describes the mechanical behavior of the actin cortex (viscoelasticity and bending rigidity). As implementation of a discrete boundary is one of the main challenges for NSPH, a boundary correction method has been validated that ensures correct mechanical interaction between the cell and the ECM model [1]. This model is used to simulate cell migration by a combination of membrane protrusion, adhesion to the ECM, contractility of the cell and local degradation of the ECM.

Results and Discussion: Various simulations of cell migration will be performed to investigate the interplay between membrane protrusion, cell-ECM adhesion, cell contraction, ECM degradation and mechanical properties of the ECM for cell migration. Figure 1 demonstrates the deformation of the ECM around a contracting cell. These simulations will be compared qualitatively with embedded cell migration data from literature and with our own experimental data of endothelial tip cell invasion in a collagen matrix during angiogenic sprouting. Displacement fields around the endothelial tip cells have been calculated and will be used to develop our model of cell migration. Together, data suggest that our cell-ECM can capture important features of single cell migration and cell-ECM interaction, and could therefore lead to a better understanding of the role of mechanics in angiogenic sprouting.

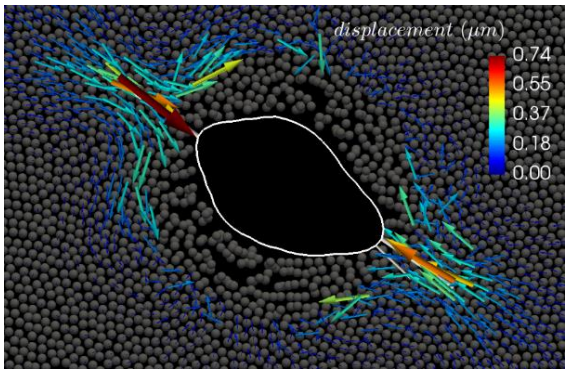

Figure 1: Displacement field in the ECM around a cell model that adheres to the ECM by protrusions on opposing sides.

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References

[1] T. Heck, et. *al.*: Modeling extracellular matrix viscoelasticity using smoothed particle hydrodynamics with improved boundary treatment. Computer Methods in Applied Mechanics and Engineering, 332:515-540, 2017.